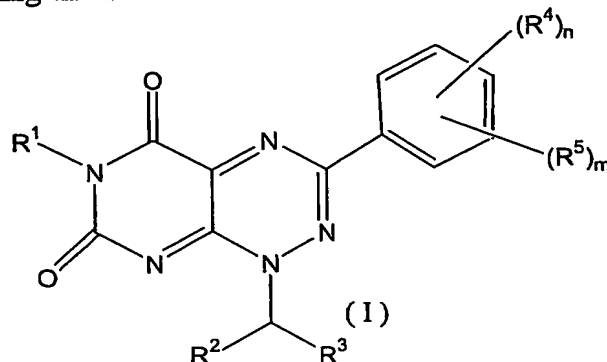


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ART 34 AMDT
(all claims)

Claims

1. A compound having the formula



the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n represents an integer being 0, 1 or 2;

10 m represents an integer being 0 or 1;

R¹ represents hydrogen, Ar¹, C₁₋₄alkyl or C₁₋₄alkyl substituted with morpholinyl or pyridinyl;

R² represents hydrogen, phenyl, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl or C₁₋₄alkyl substituted with hydroxy, phenyl or -oxy-halophenyl;

15 R³ represents hydrogen, phenyl, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl or C₁₋₄alkyl substituted with hydroxy, phenyl or -oxy-halophenyl; or

R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl or Het¹ wherein said C₃₋₈cycloalkyl or Het¹ each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, -C₁₋₄alkyl-Ar³, C₁₋₄alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or -C(=NH)-NH₂;

R⁴ represents halo, nitro, hydroxy or C₁₋₄alkyloxy;

25 R⁵ represents formyl, hydroxy, cyano, phenyl, -O-Ar², NR⁶R⁷, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylsulfonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, -O-(mono- or di(C₁₋₄alkyl)aminosulfonyl), Het², -SO₂-Het⁶, C₂₋₆alkenyl optionally substituted with phenyl,

C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, halo, Het³, NR⁶R⁷ or formyl,

C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from halo, amino, mono- or di(C₁₋₄alkyl)aminosulfonyl, aminosulfonyl, Het⁴, NR⁸R⁹ or -C(=O)-Het⁴;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl,

5 C₁₋₄alkyloxyC₁₋₄alkyl, Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, Het⁵, C₁₋₄alkyloxycarbonyl, or C₁₋₄alkylsulfonyl;

R⁸ and R⁹ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋

4alkyloxycarbonyl, Het⁷, mono- or di(C₁₋₄alkyl)aminosulphonyl or aminosulphonyl;

10 Het¹ represents piperidinyl or dihydroindenyl;

Het² represents a heterocycle selected from piperidinyl, morpholinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl;

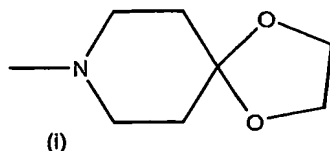
15 Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, pyrrolyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, aminosulfonyl, NR¹⁰R¹¹, imidazolyl, 20 tetrahydropyrimidinyl, amino, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

R¹⁰ and R¹¹ are each independently selected from hydrogen, C₁₋₄alkyl,

C₁₋₄alkyloxycarbonyl, aminosulfonyl, or mono- or di(C₁₋₄alkyl)aminosulfonyl;

25 Het⁴ represents a heterocycle selected from morpholinyl, piperidinyl, imidazolyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, aminosulfonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl or Het⁴ represents a monovalent radical represented by formula (i);

30



35 Het⁵ represents a heterocycle selected from pyridinyl, pyrimidinyl, pyrrolidinyl, or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each

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independently selected from C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, aminosulfonyl, C₁₋₄alkylaminosulfonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het⁶ represents morpholinyl;

Het⁷ represents pyridinyl, piperidinyl, piperazinyl or pyrimidinyl optionally substituted with C₁₋₄alkylphenyl, C₁₋₄alkyloxycarbonyl aminosulfonyl, or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Ar¹ represents an aryl substituent selected from phenyl or naphthalenyl wherein said aryl substituents each independently may optionally be substituted with one, or where possibly two or three substituents each independently selected from nitro or C₁₋₄alkyloxycarbonyl;

Ar² represents phenyl optionally substituted with one or where possible two or three substituents each independently selected from the group consisting of halo and nitro;

Ar³ represents an aryl substituent selected from the group consisting of phenyl,

2. A compound according to claim 1 wherein;

R¹ represents Ar¹, C₁₋₄alkyl preferably methyl, or C₁₋₄alkyl substituted with morpholinyl;

R² represents hydrogen or C₁₋₄alkyl;

R³ represents hydrogen or C₁₋₄alkyl; or

R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl or Het¹ wherein said C₃₋₈cycloalkyl or Het¹ each independently may optionally be substituted with C₁₋₄alkyloxycarbonyl;

R⁴ represents halo preferably chloro or R⁴ represents C₁₋₄alkyloxy preferably methoxy;

R⁵ represents C₁₋₄alkyloxycarbonyl, -O-(mono- or di(C₁₋₄alkyl)aminosulfonyl), C₁₋₄alkyl substituted with one or where possible more substituent being selected from Het³ or NR⁶R⁷,

C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from amino, Het⁴ or NR⁸R⁹;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

R⁸ and R⁹ are each independently selected from hydrogen, C₁₋₄alkyl,

C₁₋₄alkyloxycarbonyl, Het⁷ or mono- or di(C₁₋₄alkyl)aminosulphonyl;

Het¹ represents piperidinyl;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, aminosulfonyl, amino, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

Het⁵ represents pyridinyl optionally substituted with mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het⁷ represents piperidinyl optionally substituted with C₁₋₄alkylphenyl, C₁₋₄alkyloxycarbonyl, or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Ar¹ represents an aryl substituent selected from phenyl or naphthalenyl;

3. A compound according to claim 1 wherein;

R¹ represents C₁₋₄alkyl preferably methyl;

R² represents C₁₋₄alkyl preferably methyl;

R³ represents C₁₋₄alkyl preferably methyl; or

R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl preferably cyclopentyl or Het¹ preferably piperidinyl wherein said C₃₋₈cycloalkyl or Het¹ each independently may optionally be substituted with C₁₋₄alkyloxycarbonyl preferably t-butoxycarbonyl;

R⁴ represents halo or C₁₋₄alkyloxy;

R⁵ represents C₁₋₄alkyloxycarbonyl, -O-(mono- or di(C₁₋₄alkyl)aminosulfonyl), C₁₋₄alkyl substituted with one or where possible more substituent being selected from Het³ or NR⁶R⁷,

C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from amino, Het⁴ or NR⁸R⁹;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl,

C₁₋₄alkyloxyC₁₋₄alkyl, -Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, or Het⁵;

R⁸ and R⁹ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁷ or mono- or di(C₁₋₄alkyl)aminosulphonyl;

Het³ represents a heterocycle selected from piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, aminosulfonyl, amino, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

Het⁴ represents a heterocycle selected from morpholinyl, piperidinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het⁵ represents a heterocycle selected from pyridinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl, or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het⁷ represents piperidinyl.

4. A compound as claimed in any one of claims 1 to 3 wherein R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl, preferably cyclopentyl.

5. A compound according to claim 1 wherein R⁵ represents formyl, hydroxy, cyano, phenyl, -O-Ar², NR⁶R⁷, C₁₋₄alkylsulfonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, -O-(mono- or di(C₁₋₄alkyl)aminosulfonyl), Het², -SO₂-Het⁶, C₂₋₆alkenyl optionally substituted with phenyl,

C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, halo, Het³, NR⁶R⁷ or formyl, or C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from halo, amino, mono- or di(C₁₋₄alkyl)aminosulfonyl, aminosulfonyl, Het⁴, NR⁸R⁹ or -C(=O)-Het⁴;

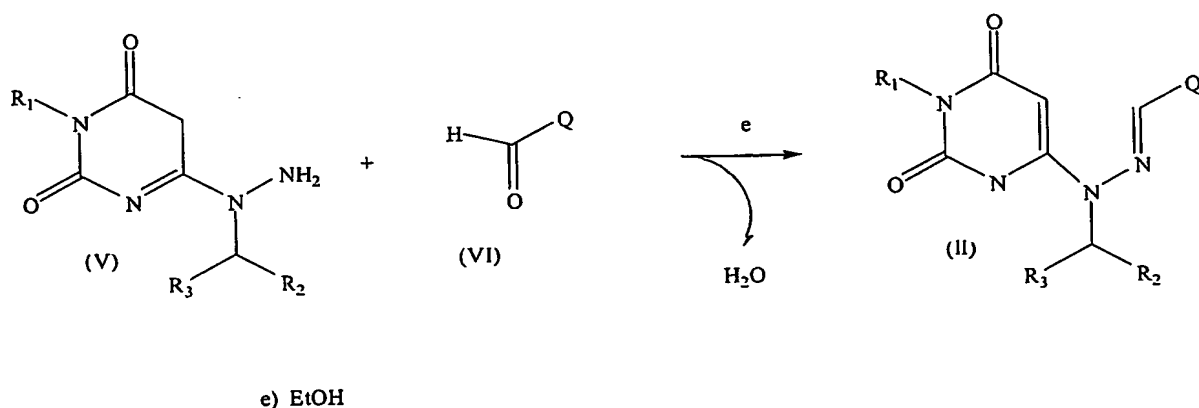
6. A compound according to claims 1 or 5 provided that when R⁵ represents NR⁶R⁷, either R⁶ or R⁷ represents C₁₋₄alkylsulfonyl or C₁₋₄alkylcarbonyl, preferably methylsulfonyl or methylcarbonyl.

7. A compound as claimed in any one of claims 1 to 5 provided that when R⁵ represents a C₁₋₄alkyloxy substituted Het⁴, said Het⁴ being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with one C₁₋₄alkyl substituent, preferably methyl, more preferably with the methyl in the para position relative to the carbon atom bearing the R⁵ substituent, or Het⁴ consists of piperazinyl substituted with one mono- or di(C₁₋₄alkyl)aminosulfonyl substituent, preferably dimethylaminosulfonyl, more preferably with the

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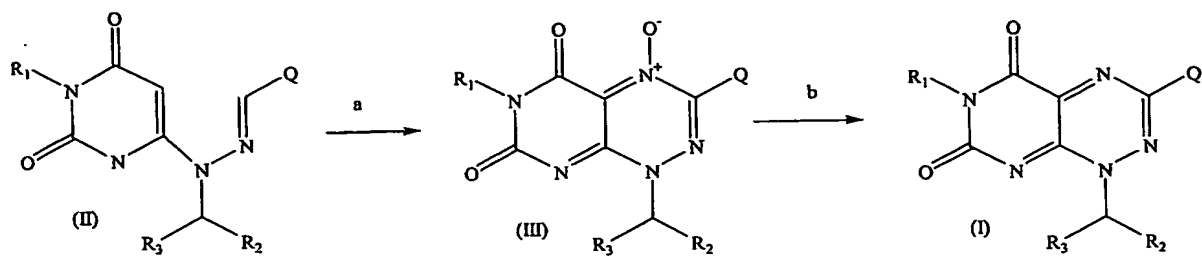
dimethylaminosulfonyl in the para position relative to the carbon atom bearing the R⁵ substituent.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of a compound as described in any one of the claims 1 to 7.
9. A process of preparing a pharmaceutical composition as defined in claim 8, characterized in that, a pharmaceutically acceptable carrier is intimately mixed with an effective kinase inhibitory amount of a compound as described in any one of claims 1 to 7.
10. A compound as claimed in any one of claims 1 to 7 for use as a medicine.
11. Use of a compound as claimed in any one of claims 1 to 7 in the manufacture of a medicament for treating cell proliferative disorders such as atherosclerosis, restinosis and cancer.
12. A process of preparing a compound as described in claim 1, characterized by i) reacting a primary amine of formula (V) with an aldehyde of formula (VI) in a condensation reaction using ethanol as a suitable solvent;



- ii) followed by a nitrosative cyclisation of the thus obtained Schiff's bases of formula (II) with NaNO₂ in acetic acid, and refluxing the nitroso intermediates of formula (III) in a suitable solvent such as acetic anhydride or ethanol further comprising dithiothreitol (DTT);

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a) NaNO_2 , AcOH , H_2O b) DTT, EtOH